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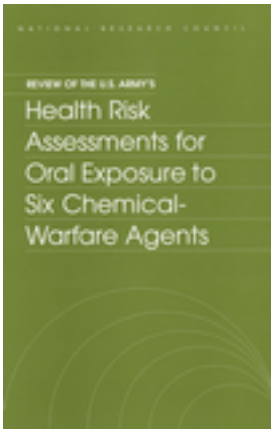

Review of the U.S. Army's Health Risk Assessments for Oral Exposure to Six Chemical-Warfare Agents

Subcommittee on Chronic Reference Doses for Selected Chemical Warfare Agents, National Research Council

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Summary

The U.S. ARMY is under a congressional mandate and the Chemical Weapons Convention of January 1993 to destroy its entire stockpile of chemical munitions. In addition to stockpiled munitions, nonstockpile chemical materiel (NSCM) has been identified for destruction. NSCM includes a host of lethal wastes from past disposal efforts, unserviceable munitions, chemically contaminated containers, chemical-production facilities, newly located chemical munitions, known sites containing substantial quantities of buried chemical weapons and wastes, and binary weapons and components. There are eight stockpile sites located in the continental United States and one on an island in the Pacific Ocean, and 82 NSCM locations have been identified. There are concerns, based on storage and past disposal practices, about soil and groundwater contamination at those sites. Six of the most commonly found chemical-warfare agents at stockpile and NSCM sites are the nerve agents GA, GB, GD, and VX and the vesicating (blistering) agents sulfur mustard and lewisite.

To ensure that chemical contamination is reduced to safe concentrations at stockpile and NSCM sites before they are used for residential, occupational, or wildlife purposes, the U.S. Army requested that health-based exposure limits for GA, GB, GD, VX, sulfur mustard, and lewisite be developed to protect the public and the environment. Oak Ridge National Laboratory (ORNL) was asked to conduct the health risk assessments and propose chronic oral reference doses (RfDs) and, where

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appropriate, oral slope factors (SFs) for the six agents. RfDs are toxicological values developed for noncancer effects and used as reference points to limit human oral exposure to potentially hazardous concentrations of chemicals thought to have thresholds for their effects. RfDs are estimates (with uncertainty spanning an order of magnitude or greater) of daily oral chemical exposures that are unlikely to have deleterious effects during a human lifetime. For chemicals identified as carcinogens (e.g., sulfur mustard), SFs are also calculated. SFs are estimates of upper-bound lifetime cancer risk from chronic exposure to an agent.

The Army's Surgeon General adopted the proposed RfDs and SFs developed by ORNL as interim values to ensure that consistent health-based criteria were applied in ongoing initiatives requiring decisions on the safety of contaminated sites. The Army's Surgeon General also requested that the NRC independently review the scientific validity of these values. The NRC assigned this task to the Committee on Toxicology (COT), and a multidisciplinary subcommittee of experts was convened to assess the scientific validity of the interim RfDs developed for GA, GB, GD, VX, sulfur mustard, and lewisite and the SF developed for sulfur mustard. Specifically, the subcommittee was asked to (1) determine whether all the relevant toxicity data were considered appropriately; (2) review the uncertainty, variability, and quality of the data; (3) determine the appropriateness of the assumptions used to derive the RfDs (e.g., the application of uncertainty factors); and (4) identify data gaps and make recommendations for future research.

Although multiple agents are present at stockpile and NSCM sites, the subcommittee was asked to evaluate the agents only on an individual basis. Furthermore, although the most likely routes of exposure to chemical-warfare agents at these sites are the inhalation and dermal routes, the subcommittee was only asked to evaluate toxicological risk from the oral route at this time. The Army is in the process of developing inhalation exposure guidelines. The subcommittee was also not asked to address issues related to risk management, such as technology, detection, and feasibility.

EVALUATION OF THE ARMY'S INTERIM RFDS AND SFS

Table S-1 presents the interim RfDs and SFs adopted by the Army for GA, GB, GD, VX, sulfur mustard, and lewisite, as well as the recommenda

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tions of the subcommittee. The subcommittee found that the guidelines used to derive the Army's interim RfDs were consistent with guidelines used by the U.S. Environmental Protection Agency (EPA) and were appropriate. In general, the approach was to identify the no-observed-adverse-effect level (NOAEL) or the lowest-observed-adverse-effect level (LOAEL) from animal or human studies. The NOAEL or LOAEL was divided by an overall uncertainty factor that reflects the uncertainties associated with the types of data used and a professional judgment of the entire data base for the chemical. An SF for sulfur mustard was derived using a comparative potency method.

TABLE S-1 Reference Doses and Slope Factors for Six Chemical-Warfare Agents

Agent	Army's Interim RfDs (mg/kg/d)	NRC's Recommended RfDs (mg/kg/d)	Army's Interim SFs (per mg/kg/d)	NRC's Recommended SFs (per mg/kg/d)
GA	4×10^{-5}	4×10^{-5}	NA	NA
GB	2×10^{-5}	2×10^{-5}	NA	NA
GD	4×10^{-6}	4×10^{-6}	NA	NA
VX	6×10^{-7}	5×10^{-7}	NA	NA
Sulfur mustard	7×10^{-6}	7×10^{-6}	9.5	1.6
Lewisite	1×10^{-4}	1×10^{-5}	NA	NA

Abbreviations: RfDs, reference doses; SFs, slope factors; NA, not applicable.

The subcommittee determined that the Army's interim RfDs for GA, GB, GD, and sulfur mustard were scientifically valid but concluded that the RfDs for VX and lewisite and the SF for sulfur mustard were too high. The bases for those conclusions are described below. Research recommendations for filling major data gaps are also presented.

CONCLUSIONS AND RECOMMENDATIONS

GA

The Army's interim RfD of 4×10^{-5} mg/kg of body weight per day for GA was based on a subchronic intraperitoneal toxicity study in rats, in which depression in plasma-cholinesterase (ChE) activity was considered the

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critical end point. Although that end point is considered a biomarker of exposure rather than an adverse effect, the subcommittee agrees that the study is the best available one to use for deriving the RfD for GA and concludes that the available data on GA support the proposed RfD.

The major gap in the available information on GA is the lack of either a subchronic or a chronic oral toxicity study from which to derive the RfD. The absence of oral data could be addressed by conducting a subchronic oral toxicity study that assesses anti-ChE activity in red blood cells (RBCs) and plasma in one or preferably two species. If further research reveals that significant toxic effects can be induced by any of the nerve agents at doses below those that cause significant ChE inhibition, additional studies should be conducted to reassess the safety of the recommended RfD for GA.

GB

The Army's interim RfD of 2×10^{-5} mg/kg per day for GB was based on a subchronic oral toxicity study in rats, in which depression in RBC-ChE activity was considered the critical end point. Although that end point is a biomarker of exposure rather than an adverse effect, the subcommittee believes that this study is the best available one from which to derive the RfD for GB and concludes that the proposed RfD is scientifically valid.

The major gap in the available information on GB is the lack of either a subchronic or a chronic oral toxicity study that demonstrates a clear LOAEL or NOAEL. The absence of that type of data could be addressed by conducting a subchronic oral toxicity study that assesses anti-ChE activity in RBCs and plasma in one or preferably two species. If further research reveals that significant toxic effects can be induced by any of the nerve agents at doses below those that cause significant ChE inhibition, additional studies should be conducted to reassess the safety of the recommended RfD for GB.

GD

The Army's interim RfD of 4×10^{-6} mg/kg per day for GD was based on a subchronic oral toxicity study in rats, in which depression of plasma-

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ChE activity was observed. Although that end point is a biomarker of exposure rather than an adverse effect, the subcommittee believes that this study is the best available one from which to derive the RfD for GD and concludes that the proposed RfD is scientifically valid.

The major gap in the available information on GD is the lack of either a subchronic or a chronic oral toxicity study that demonstrates a clear dose-response relationship between GD exposure and ChE inhibition. The absence of that type of data could be addressed by conducting a subchronic oral toxicity study that assesses anti-ChE activity in RBCs and plasma in one or preferably two species. Range-finding studies focusing on ChE analytical methods offer the best possibility for filling the data gap. If further research reveals that significant toxic effects can be induced by any of the nerve agents at doses below those that cause significant ChE inhibition, additional studies should be conducted to reassess the safety of the recommended RfD for GD.

VX

The Army's interim RfD of 6×10^{-7} mg/kg per day for VX was based on an oral toxicity study in sheep, in which depression in blood-ChE activity was observed. After evaluating that study, the subcommittee concludes that uncertainties about the relevance of this animal model to humans and weaknesses in the study design undermine the use of the study for deriving the RfD. Instead, the subcommittee recommends using a 1964 study of human volunteers in whom depression in RBC ChE was observed after oral exposure to low concentrations of VX. Although that study also has weaknesses and involves a biomarker of exposure rather than an adverse effect, the subcommittee believes it is preferable to use human data rather than data from a questionable animal model, because the uncertainty associated with extrapolating from animals to humans is avoided. On the basis of the human study, the subcommittee concludes that the data on VX support an RfD of 5×10^{-7} mg/kg per day, which is slightly lower than the Army's interim RfD of 6×10^{-7} mg/kg per day.

The major gap in the available information on VX is the lack of either a subchronic or a chronic oral toxicity study that demonstrates a clear dose-response relationship between VX exposure and ChE inhibition. The absence of that type of data could be addressed by conducting a

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subchronic oral toxicity study that assesses anti-ChE activity in RBCs and plasma in one or preferably two species. If further research reveals that significant toxic effects can be induced by any of the nerve agents at doses below those that cause significant ChE inhibition, additional studies should be conducted to reassess the safety of the recommended RfD for VX.

SULFUR MUSTARD

The Army's interim RfD of 7×10^{-6} mg/kg per day for sulfur mustard was based on an oral two-generation reproductive toxicity study in rats, in which thickening of the forestomach epithelium was observed. The subcommittee agrees that this study is the best available one from which to derive the RfD for sulfur mustard and concludes that the interim RfD for sulfur mustard is scientifically valid. However, the subcommittee recommends adjustments in two of the uncertainty factors used to derive that RfD. Although the adjustments do not change the RfD for sulfur mustard, the subcommittee believes that they are scientifically justified and should be reflected in the Army's supporting documentation for the RfD.

Sulfur mustard is the only agent in this report associated with sufficient evidence of carcinogenicity in animal studies and, therefore, is the only agent for which a carcinogenic SF was derived. The indirect approach used to estimate the SF involved comparing the carcinogenic potency of sulfur mustard to that of the well-known carcinogen benzo[α]pyrene (B[α]P). Although the subcommittee finds that approach to be scientifically valid, given the absence of either a epidemiological investigation or a chronic oral animal bioassay on sulfur mustard, it recommends the use of a more recent risk estimate of the carcinogenic potency of B[α]P. On the basis of that estimate, the subcommittee concludes that the Army's interim SF of 9.5 per milligram per kilogram per day should be lowered to 1.6 per milligram per kilogram per day. Thus, if the potential carcinogenic risk from ingestion of sulfur mustard is restricted to less than 1 in 100,000 persons, daily oral doses should be limited to 6×10^{-6} mg/kg per day, a value slightly lower than the Army's interim RfD of 7×10^{-6} mg/kg per day.

The major gap in the available information on sulfur mustard is the lack of a chronic oral animal bioassay from which to derive the RfD and

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SF. Because of that deficiency, the RfD for sulfur mustard is estimated by extrapolating from a subchronic study in animals, and the SF is established by applying comparative carcinogenic potency methods. The absence of chronic oral toxicity data can be addressed by conducting a chronic oral animal bioassay. It is important that sulfur mustard be delivered to animals at a slow rate (i.e., in the diet) rather than by stomach tube, because it is corrosive at the point of entry.

LEWISITE

The Army's interim RfD of 1×10^{-4} mg/kg per day for lewisite was based on two oral studies: a two-generation reproductive study and a 90-day toxicity study in rats. In both studies, necrosis and hyperplasia of the forestomach were observed. After considering those studies and other potential studies, the subcommittee concludes that a 1987 teratogenicity study conducted in rabbits is more appropriate than the rat studies for deriving the RfD, because there is evidence that the rabbit might be more susceptible to lewisite than the rat. On the basis of the rabbit study, in which maternal mortality and gastric lesions were observed, the subcommittee believes that the RfD for lewisite should be lowered from 1×10^{-4} mg/kg per day to 1×10^{-5} mg/kg per day.

The major gaps in the available information on lewisite are the lack of information on the implications of administering lewisite directly to the stomach over a short time and the absence of chronic oral toxicity data from which to derive an RfD. Because of those deficiencies, the RfD for lewisite was estimated by extrapolating from a less-than-ideal animal study to humans. Confidence in the RfD can be increased if subchronic oral toxicity studies in rabbits and rats are conducted to compare the effects of chronic oral exposure to low concentrations of lewisite with the effects of short-term intragastric administration of small volumes of lewisite. Such studies will provide not only the data needed to better understand the implications of dosing techniques but also more pertinent information on whether the rabbit is more appropriate than the rat for deriving an RfD for lewisite.

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Committee on Toxicology
Board on Environmental Studies and Toxicology
Commission on Life Sciences
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SUBCOMMITTEE ON CHRONIC REFERENCE DOSES FOR SELECTED CHEMICAL-WARFARE AGENTS

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Preface

Several military bases contaminated with chemical-warfare agents as a result of storage and past disposal practices are slated to be closed pursuant to the Base Realignment and Closure Act. Before those military bases can be transferred to civilian use, contaminated soil and water must be cleaned to levels that are considered safe. To help make decisions on restoration required at contaminated sites and on the potential uses of the former military installations (e.g., for housing, occupational, or wildlife purposes), the U.S. Army developed interim chronic oral reference doses and, where appropriate, oral slope factors for six chemical-warfare agents that are likely to be encountered at contaminated sites. Similar information for inhalation exposure is under development.

In this report, the Subcommittee on Chronic Reference Doses for Selected Chemical-Warfare Agents of the National Research Council's (NRC's) Committee on Toxicology reviews the scientific validity of the Army's interim values for the six chemical-warfare agents—GA, GB, GD, VX, sulfur mustard, and lewisite. The NRC report is intended to be useful to the Army in making site-specific cleanup decisions.

This report has been reviewed in draft form by individuals chosen for their technical expertise and diverse perspectives in accordance with procedures approved by the NRC's Report Review Committee for reviewing NRC and Institute of Medicine reports. The purpose of that independent review was to provide candid and critical comments to assist the NRC in making the published report as sound as possible and to ensure

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that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals, who are neither officials nor employees of the NRC, for their participation in the review of this report: Joseph Borzelleca, Virginia Commonwealth University; John Doull, University of Kansas Medical Center; Ronald W. Estabrook (report review committee monitor), University of Texas Southwestern Medical Center; Florence Kinoshita, Hercules Inc.; Loren Koller (report review coordinator), Oregon State University; John O'Donoghue, Eastman Kodak Company; and Joseph Rodricks, Life Sciences Trust.

The individuals listed above have provided many constructive comments and suggestions. It must be emphasized, however, that responsibility for the final content of this report rests entirely with the authoring committee and the NRC.

We gratefully acknowledge Veronique Hauschild, Joe King, and Steve Kistner (all of the U.S. Army Center for Health Promotion and Preventive Medicine) and Dennis Opresko, Robert Ross, Annetta Watson, and Robert Young (all of Oak Ridge National Laboratory) for providing background information and for making presentations to the subcommittee.

We are grateful for the assistance of the NRC staff for preparing the report. Staff members who contributed to this effort are James J. Reisa, director of the Board on Environmental Studies and Toxicology; Carol A, Maczka, senior program director for toxicology and risk assessment; Ruth E. Crossgrove, editor; and Linda Leonard, senior project assistant. We especially wish to recognize the major contributions of the project director, Kulbir S. Bakshi, and the program officer, Susan N.J. Pang, who directed the preparation of the subcommittee's report. Their knowledge of the scientific and technical literature and their tireless effort to obtain information and to organize the subcommittee meetings and the report aided in the successful completion of the project.

Finally, we would like to thank all the members of the subcommittee for their dedicated efforts throughout the development of this report.

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